1. PRODUCT NAME

Ibuprofen (Ethics) 100 mg/5 mL oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ibuprofen 100 mg/5 mL; each 5 mL of oral suspension contains 100 mg of ibuprofen.

3. PHARMACEUTICAL FORM

Ibuprofen oral suspension is a white, orange flavoured suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Temporary relief of discomfort and pain associated with teething, toothache, headache, earache, sore throat, immunization, cold and flu symptoms and muscular aches and pain.

4.2 Dose and method of administration

The dose should be individualised after assessing the risk/benefit ratio such that the lowest effective dose for the shortest possible duration is used.

Shake bottle well before use.

Infants and children

For infants and children a daily oral dose of 10 mg/kg body weight in divided doses up to 40 mg/kg body weight in divided doses may be recommended in cases of juvenile rheumatoid arthritis.

Age	Average weight	Recommended dose
3-6 months	6-8 kg	3-4 mL
6-12 months	8-10 kg	4-5 mL
1-3 years	10-14 kg	5-7 mL
3-5 years	14-18 kg	7-9 mL
5-7 years	18-22 kg	9-11 mL
7-9 years	22-28 kg	11-14 mL
9-12 years	28-40 kg	14-20 mL

In children weighing less than 30 kg, the total daily dose of Ibuprofen Oral Suspension should not exceed 500 mg.

Adults

Although Ibuprofen tablets are generally used for adults, when there are swallowing difficulties, Ibuprofen Oral Suspension can be used at an appropriate dosage.

The initial recommended dosage is 1200 - 1800 mg (60 – 90 mL) daily in divided doses. Some patients can be maintained on 600 - 1200 mg (30 mL – 60 mL) daily. In severe or acute conditions it can be advantageous to increase the dosage until the acute phase is brought under control, providing that the total daily dosage does not exceed 2400 mg (120 mL) in divided doses.

Elderly

Elderly patients are more prone to adverse effects. Caution must be taken with dosage in this group and also in patients with renal impairment or impaired liver function.

4.3 Contraindications

- Known hypersensitivity to ibuprofen or any of the excipients listed in section 6.1
- Hypersensitivity (e.g. asthma, rhinitis or urticaria) to aspirin or other nonsteroidal anti-inflammatory drugs
- As with other nonsteroidal anti-inflammatory agents, ibuprofen should not be used in active gastrointestinal bleeding or in the presence of peptic ulceration
- History of gastrointestinal bleeding or perforation, related to previous NSAID therapy
- Severe heart failure
- Severe liver failure
- Severe renal failure (glomerular filtration below 30 mL/min)
- During the third trimester of pregnancy
- Pregnancy
- Lactation

4.4 Special warnings and precautions for use

Gastrointestinal events

All NSAIDs can cause gastrointestinal discomfort and rarely, serious potentially fatal gastrointestinal effects e.g. ulcers, bleeding and perforations, which may increase with dose or duration of use but may occur at any time without warning. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% patients treated for one year. These trends continue with longer duration of use increasing the likelihood of developing a serious GI event at some time during the course of therapy. However even short term therapy is not without risk.

Caution is advised in patients with risk factors for GI events who may be at greater risk of developing serious GI events e.g. the elderly, those with a history of serious GI events, smoking and alcoholism. When GI bleeding or ulcerations occur in patients receiving NSAIDs the medicine should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious GI toxicity.

The concurrent use of aspirin and NSAIDs also increases the risk of serious GI adverse events.

Respiratory disorder

Caution is required if ibuprofen is administered to patients suffering from, or with a previous history of, bronchial asthma, chronic rhinitis or allergic diseases since ibuprofen has been reported to cause bronchospasm, urticarial or angioedema in such patients.

Ophthalmological effects

Adverse ophthalmological effects have been observed with nonsteroidal anti-inflammatory agents; accordingly, patients who develop visual disturbances during treatment with ibuprofen should have an ophthalmological examination.

Impaired liver function or a history of liver disease

Patients with impaired liver function or a history of liver disease who are on long term ibuprofen therapy should have hepatic function monitored at regular intervals. Ibuprofen has been reported to have a minor and transient effect on liver enzymes.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, though rare, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If abnormal liver tests persist or worsen, or if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), ibuprofen should be discontinued.

Impaired renal function

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration. There is a risk of renal impairment especially in dehydrated children and adolescents.

The two major metabolites of ibuprofen are excreted mainly in the urine and impairment of renal function may result in their accumulation. The significance of this is unknown. NSAIDs have been reported to cause nephrotoxicity in various forms; interstitial nephritis, nephrotic syndrome and renal failure. In patients with renal, cardiac or hepatic impairment, those taking diuretics and ACE Inhibitors, and the elderly, caution is required since the use of NSAIDs may result in deterioration of renal function. The long term concomitant intake of various analgesics further increases the risk. For patients with renal, hepatic or cardiac impairment, use the lowest effective dose, for the shortest possible duration and monitor renal function especially in long term treated patients.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics:

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist, an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the initiation of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Cardiovascular thrombotic events

Epidemiological data suggest that use of ibuprofen, particularly at a high dose (2400 mg/daily) and in long term treatment, may be associated with a small increased risk of arterial thrombotic

events such as myocardial infarction or stroke. Overall, epidemiological studies do not suggest that low dose ibuprofen (1200 mg/daily) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

There is no consistent evidence that concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Heart failure

Fluid retention and oedema have been reported in association with ibuprofen, therefore, the drug should be used with caution in patients with a history of failure or hypertension.

Hypertension

NSAIDs may lead to the onset of hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Severe skin reactions

NSAIDs may very rarely cause serious cutaneous adverse events e.g. exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) which can be fatal and occur without warning. These serious events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other hypersensitivity.

Aseptic meningitis

Aseptic meningitis has been reported only rarely, usually but not always in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

Haematological monitoring

Blood dyscrasias have been rarely reported. Patients on long-term therapy with ibuprofen should have regular haematological monitoring.

Coagulation defects

Like other NSAIDs, ibuprofen can inhibit platelet aggregation. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulation therapy.

Masking signs of infection

As with other drugs of this class, ibuprofen may mask the usual signs of infection.

Infections and infestations
Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of Ibuprofen the patient is therefore recommended to go to a doctor without delay.

Special precautions

Withdrawal of concomitant steroid therapy
In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

4.5 Interaction with other medicines and other forms of interaction
Concurrent use of NSAIDs and warfarin has been associated with severe sometimes fatal haemorrhage. The mechanism of this interaction is not known but may involve increased bleeding from NSAID-induced gastrointestinal ulceration or an additive effect of NSAID inhibition of platelet function with the anticoagulant effect of warfarin. Ibuprofen should only be used in patients taking warfarin if absolutely necessary. Patients taking this combination must be closely monitored.

Ibuprofen has been shown to decrease the renal clearance and increase plasma concentrations of lithium. Lithium plasma concentrations should be monitored in patients on concurrent ibuprofen therapy.

Ibuprofen like other NSAIDs can reduce the antihypertensive effect of ACE inhibitors and β-blockers with possible loss of blood pressure control and can attenuate the natriuretic effects of thiazide diuretics and frusemide.

NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma cardiac glycoside levels. Care should therefore be taken in patients treated with cardiac glycosides.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)
Increased risk of gastrointestinal bleeding.

Aminoglycosides
NSAIDs may decrease the excretion of aminoglycosides.

Cholestyramine
The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.

Corticosteroids
Increased risk of gastrointestinal bleeding.

Herbal extracts
Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

Other analgesics
Avoid concomitant use of two or more NSAIDs, including aspirin and cyclooxygenase-2 (COX-2) selective inhibitors, because of the potential of increased adverse effects. Ibuprofen antagonizes the irreversible inhibition of platelet cox-1 induced by low dose aspirin. To reduce this effect, ibuprofen should be administered at least 8 hours before or 30 minutes after taking low dose aspirin.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5).

Cyclosporine or tacrolimus
Increased risk of nephrotoxicity when used with NSAIDs.

Mifepristone
NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Quinolone antibiotics
Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Sulfonylureas
NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

Zidovudine
Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and hematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Methotrexate
NSAIDs inhibit tubular secretion of methotrexate in animals. As a result, reduction of clearance of methotrexate may occur. Use of high doses of methotrexate concomitant with NSAIDs should be avoided. At low doses of methotrexate caution should be used if ibuprofen is administered concomitantly.

CYP2C9 Inhibitors
Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+)-ibuprofen exposure by approximately 80 to 100% has been shown. Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

4.6 Fertility, pregnancy and lactation

Female fertility

The use of ibuprofen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.

Pregnancy (Category C)

While no teratogenic effects have been demonstrated in animal studies, the use if ibuprofen during pregnancy should be avoided if possible. Congenital abnormalities have been reported in association with ibuprofen administration in man; however these are low in frequency and do not appear to follow any discernible pattern. Nonsteroidal anti-inflammatory drugs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation and delay labour and birth. Continuous treatment with nonsteroidal anti-inflammatory drugs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

Lactation

Ibuprofen is not recommended for nursing mothers unless the expected benefits to the mother outweigh the potential risk to the neonate.

4.7 Effects on ability to drive and use machines

Following treatment with ibuprofen, the reaction time of patients may be affected. NSAIDs may cause dizziness, drowsiness, fatigue and visual disturbances. If affected patients should not drive or operate machinery.

4.8 Undesirable effects

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of non-specific allergic reaction and anaphylaxis, respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and very rarely, , bullous dermatoses (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme).

More common reactions: (greater than 1%)

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Gastrointestinal complaints include nausea, epigastric pain, heartburn, diarrhoea, abdominal distress, nausea and vomiting, dyspepsia, constipation, abdominal cramps or pain, gastrointestinal haemorrhage, haematemesis, melaena, fullness of the GI tract (bloating and flatulence).

Ear and labyrinth disorders: Tinnitus, hearing impaired.

General disorders and administration site conditions: Oedema, fluid retention; fluid retention generally responds promptly to discontinuation of the drug.

Nervous system disorders: Dizziness, headache, nervousness.

Skin and subcutaneous tissue disorders: Rash (including maculopapular type), pruritus.

General disorders: Decreased appetite, fatigue.

Less common reactions: (less than 1%)

Nervous system disorders: Depression, insomnia, anxiety, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma.

Skin and subcutaneous tissue disorders: Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia.

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, mouth ulceration, ulcerative stomatitis, pancreatitis, gastritis.

Hepatobiliary disorders: hepatitis, jaundice, abnormal liver function.

Blood and lymphatic system disorders: Neutropenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia and decrease in haemoglobin and haematocrit.

Cardiac disorders: Cardiac failure, myocardial infarction.

Vascular disorder: Hypertension.

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm, dyspnoea.

Infections and infestations: Rhinitis and meningitis aseptic

Eye disorders: Amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision) have occurred but is usually reversed after cessation of therapy. Any patient with eye complaints should have an ophthalmological examination which includes central vision fields (see section 4.4). Visual impairment and toxic neuropathy have also been reported

Allergic: Syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis

Precise Incidence Unknown (but less than 1%) Causal Relationship Unknown

Nervous system disorders: Paraesthesias, hallucinations, dream abnormalities, vertigo.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, photoallergic skin reactions.

Eye disorders: Conjunctivitis, diplopia, optic neuritis, cataracts.

Blood and lymphatic system disorders: Bleeding episodes (eg epistaxis, menorrhagia).

Metabolism and nutrition disorders: Gynaecomastia, hypoglycaemic reaction, acidosis.

Renal and urinary disorders: Renal nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

Hepatobiliary disorders: Abnormal liver function, hepatic failure, hepatitis and jaundice.

Cardiac disorders: Arrhythmias (sinus tachycardia, sinus bradycardia).

Immune system disorders: Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema.

Additional post-marketing adverse reactions

Gastrointestinal: Exacerbation of colitis and Crohn's Disease (see section 4.1). Pancreatitis has been reported very rarely.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms
Symptoms include nausea, abdominal pain and vomiting, dizziness and rarely loss of consciousness.

Clinical features of overdose with ibuprofen which may result are depression of the central nervous system and the respiratory system.

Treatment
Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount of ibuprofen, use of activated charcoal should be considered. Alternatively in adults gastric lavage may be considered for potentially life-threatening overdoses.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Actions
Ibuprofen is a nonsteroidal anti-inflammatory agent (NSAID) that possesses analgesic and antipyretic activities. Its mode of action, like that of other nonsteroidal anti-inflammatory agents, is not completely understood, but may be related to prostaglandin synthetase inhibition.

Ibuprofen has shown anti-inflammatory, analgesic and antipyretic activity in both animal and human studies. These properties provide symptomatic relief of inflammation and pain in rheumatoid arthritis, osteoarthritis and allied conditions.

5.2 Pharmacokinetic properties

Absorption
Ibuprofen is well absorbed after oral administration. Single doses of 200 mg taken on an empty stomach by volunteers produced peak serum levels after approximately 45 minutes. When taken after food, absorption was slower, peak levels appearing at 1.5 to 3 hours.

Bioavailability
The bioavailability of ibuprofen from one 400 mg tablet is equivalent to that from two 200 mg tablets, and 20 mL of a 2% Ibuprofen Oral Suspension.

Distribution
Apparent volume of distribution is 0.14 L/kg. Ibuprofen and its metabolites readily cross the placental barrier in pregnant rabbits and rats. It is not known if ibuprofen enters the CSF. According to reports only minimal amounts are excreted in breast milk.

Protein binding
99% of ibuprofen is protein bound. The high protein binding of ibuprofen should be borne in mind when prescribing ibuprofen together with other protein bound drugs which bind to the same site on human serum albumin.

Metabolism
About 90% of ibuprofen is metabolised to two major metabolites, A ((+) 2-4-(2-hydroxy-2-methylpropylphenyl) propionic acid) and B ((+) 2-4-(2-carboxypropylphenyl) propionic acid). Both metabolites are dextrorotatory and are devoid of anti-inflammatory and analgesic activity.

Normal volunteers and patients with rheumatoid arthritis were given ibuprofen 800 mg as a single dose. After 14 to 24 hours the plasma levels of ibuprofen and metabolites were less than 0.25 µg/mL.

Excretion
The kidney is the major route of excretion. 95% of ibuprofen was excreted in the urine within 24 hours of a single dose of 500 mg; 35% as metabolite A (15 % free, 20% conjugated), 51% as metabolite B (42% free, 9% conjugated), ibuprofen 9% (1% free, 8% conjugated).

Half-life
Plasma half-life of ibuprofen is in the range 1.9 to 2.2 hours.

5.3 Preclinical safety data
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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Citric acid monohydrate
- Dispersible cellulose

- Maltitol
- Orange flavour 4051
- Orange flavour sweet no.1
- Polysorbate 80
- Purified water
- Saccharin sodium
- Sodium benzoate
- Sodium citrate dihydrate
- Sodium methyl hydroxybenzoate
- Sodium propyl hydroxybenzoate
- Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25°C, protect from light.

6.5 Nature and contents of container

Prescription: 500 mL PET bottle with a child resistant cap.

Pharmacy only medicine (dispensing pack): 200 mL amber coloured PET bottle with a child resistant cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine: 500 mL bottle

Pharmacy only medicine (dispensing pack): 200 mL bottle

8. SPONSOR

Multichem NZ Ltd
Private Bag 93527
Takapuna

Auckland 0740
Telephone: (09) 488 0330

9. DATE OF FIRST APPROVAL

Prescription medicine: 26 September 2013

Pharmacy only medicine: 25 November 2010

10. DATE OF REVISION OF THE TEXT

04 February 2020

SUMMARY TABLE OF CHANGES

Section	Changes
3, 6.3, 6.5 7, 8, 9	Editorial changes to improve readability
4.3-4.9	Changes requested by Medsafe